



Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number:

0 376 534
A1

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 89312885.0

(51) Int. Cl.⁵: **A61K 31/47, A61K 47/12,**
A61L 15/16

(22) Date of filing: **11.12.89**

(30) Priority: **15.12.88 US 284933**

(43) Date of publication of application:
04.07.90 Bulletin 90/27

(84) Designated Contracting States:
BE CH DE ES FR GB IT LI NL SE

(71) Applicant: **RIKER LABORATORIES, INC.**
3M Center - 225-1S-07
Saint Paul Minnesota 55144(US)

(72) Inventor: **Wick, Steven M. c/o Riker Laboratories, Inc.**
3M Center Building 225-1S-07
St. Paul Minnesota 55144(US)
Inventor: **Schultz, Helen Jensen c/o Riker Laboratories, Inc.**
3M Center Building 225-1S-07
St. Paul Minnesota 55144(US)
Inventor: **Nelson, Gregory R. c/o Riker Laboratories, Inc.**
3M Center Building 225-1S-07
St. Paul Minnesota 55144(US)
Inventor: **Mitra, Amit K. c/o Riker Laboratories, Inc.**
3M Center Building 225-1S-07
St. Paul Minnesota 55144(US)
Inventor: **Berge, Stephen M. c/o Riker Laboratories, Inc.**
3M Center Building 225-1S-07
St. Paul Minnesota 55144(US)

(74) Representative: **Baillie, Iain Cameron et al**
c/o Ladas & Parry Isartorplatz 5
D-8000 München 2(DE)

A1

(54) **Topical formulations and transdermal delivery systems containing 1-isobutyl-1H-imidazo[4,5-c]quinoline-4-amine.**

(57) Pharmaceutical formulations and adhesive-coated sheet materials for the topical and/or transdermal delivery of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, including creams, ointments and pressure-sensitive adhesive compositions. Pharmacological methods of using the formulations and the adhesive-coated sheet materials of the invention in the treatment of viral infections.

EP 0 376 534

TOPICAL FORMULATIONS AND TRANSDERMAL DELIVERY SYSTEMS CONTAINING 1-ISOBUTYL-1H-IMIDAZO[4,5-c]QUINOLIN-4-AMINE

BACKGROUND OF THE INVENTION

5

Field of the Invention

This invention pertains to pharmaceutical formulations for the topical or transdermal delivery of drugs. More particularly, it pertains to creams, ointments, pressure sensitive adhesive coatings, and adhesive-coated sheet materials that contain compounds that enhance skin penetration of drugs.

Description of the Related Art

15

The compound 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine is disclosed in U.S. Pat. No. 4,689,338 and described therein as an antiviral agent and as an interferon inducer. A variety of formulations for topical administration of this compound are also described.

U.S. Pat. No. 4,751,087 discloses the use of a combination of ethyl oleate and glyceryl monolaurate as a skin penetration enhancer for nitroglycerine, with all three components being contained in the adhesive layer of a transdermal patch.

U.S. Pat. No. 4,411,893 discloses the use of N,N-dimethyldodecylamine-N-oxide as a skin penetration enhancer in aqueous systems.

U.S. Pat. No. 4,722,941 discloses readily absorbable pharmaceutical compositions that comprise a pharmacologically active agent distributed in a vehicle comprising an absorption-enhancing amount of at least one fatty acid containing 6 to 12 carbon atoms and optionally a fatty acid monoglyceride. Such compositions are said to be particularly useful for increasing the absorption of pharmacologically active bases.

U.S. Pat. No. 4,746,515 discloses a method of using glyceryl monolaurate to enhance the transdermal flux of a transdermally deliverable drug through intact skin.

SUMMARY OF THE INVENTION

35

The present invention provides a substantially non-irritating pharmaceutical formulation for topical and/or transdermal administration of the agent 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, which formulation comprises:

a) 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine in an amount of about 0.5 percent to about 9 percent by weight based on the total weight of the formulation; and

b) a pharmaceutically acceptable vehicle for the 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, which vehicle comprises a fatty acid selected from the group consisting of isostearic acid, oleic acid and a combination thereof in a total amount of about 3 percent to about 45 percent by weight based on the total weight of the formulation. The formulation is further characterized in that when tested in the hairless mouse skin model described herein, the formulation provides a penetration of the agent of at least about 10% (and preferably at least about 15 %) of the total amount of the agent contained in the formulation in 24 hours.

The salient elements of a pharmaceutical formulation according to the invention are (a) 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine and (b) a fatty acid, i.e., isostearic and/or oleic acid. A pharmaceutical formulation of the invention can be in any form known to the art, such as a cream, an ointment, or a pressure-sensitive adhesive composition, each form containing the necessary elements in particular amounts and further containing various additional elements.

A cream of the invention preferably contains about 1 percent to about 5 percent by weight of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, based on the total weight of the cream; about 5 percent to about 25 percent by weight of fatty acid, based on the total weight of the cream; and optional ingredients such as

emollients, emulsifiers, thickeners, and/or preservatives.

An ointment of the invention contains an ointment base in addition to 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine and fatty acid. An ointment of the invention preferably contains about 0.5 percent to about 9 percent, and more preferably about 0.5 percent to about 5 percent by weight 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine; about 3 percent to about 45 percent, more preferably about 3 percent to about 25 percent by weight fatty acid; and about 60 percent to about 95 percent by weight ointment base, all weights being based on the total weight of the ointment. Optionally, an ointment of the invention can also contain emulsifiers, emollients and thickeners.

A pressure-sensitive adhesive composition of the invention contains 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, fatty acid, and an adhesive. The adhesives utilized in a pressure sensitive adhesive composition of the invention are preferably substantially chemically inert to 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine. A pressure sensitive adhesive composition of the invention preferably contains about 0.5 percent to about 9 percent by weight, more preferably of about 3 percent to about 7 percent by weight 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine; about 10 percent to about 40 percent by weight, more preferably of about 15 percent to about 30 percent by weight, and most preferably about 20 percent to about 30 percent by weight of fatty acid; all weights being based on the total weight of the pressure sensitive adhesive composition.

Optionally, pressure sensitive adhesive compositions of the invention can also contain one or more skin penetration enhancers. The total amount of skin penetration enhancer(s) present in a pressure sensitive adhesive composition of the invention is preferably about 3 percent to about 25 percent by weight, and more preferably about 3 percent to about 10 percent by weight based on the total weight of the pressure sensitive adhesive composition.

A pressure sensitive adhesive coated sheet material of the invention can be made from a pressure-sensitive adhesive composition of the invention in the form of an article such as a tape, a patch, a sheet, or a dressing.

A formulation of the invention can be used to topically and/or transdermally administer 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine for treating viral infections, for example Type I or Type II Herpes simplex infections.

30

BRIEF DESCRIPTION OF THE DRAWING

The invention will be described below with reference to the accompanying Drawing, which is an isometric view of a diffusion cell for measuring penetrability of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine across mammalian skin.

40

DETAILED DESCRIPTION OF THE INVENTION

45

As used in the specification and claims, the phrase "substantially non-irritating" designates formulations that do not cause unacceptable skin irritation in conventional repeat skin irritation tests in albino rabbits such as that described in Draize et al., "Appraisal of the Safety of Chemicals in Food, Drugs and Cosmetics", prepared by the Division of Pharmacology of the Food and Drug Administration, published originally in 1959 by the Association of Food and Drug Officials of the United States, Topeka, Kansas (2nd printing 1965).

The present invention provides pharmaceutical formulations such as creams, ointments and adhesive coatings that contain 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine and a fatty acid such as isostearic and/or oleic acid. The formulations of the invention provide desirable skin penetrability of the 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine.

The compound 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine is a known antiviral agent that is also known to induce interferon biosynthesis. It can be prepared using the method disclosed in U.S. Pat. No. 4,689,338. The compound can be used to treat viral infections such as Type I or Type II Herpes simplex infections and genital warts. Furthermore, the fact that the compound is an interferon inducer suggests that it, and therefore formulations containing it, might be useful in the treatment of numerous other diseases, such as rheumatoid arthritis, warts, eczema, hepatitis B, psoriasis, multiple sclerosis, essential thrombocythaemia, and cancer, such as basal cell carcinoma and other neoplastic diseases. The amount of 1-

isobutyl-1H-imidazo[4,5-c]quinolin-4-amine present in a formulation of the invention will be an amount effective to treat the targeted disease state to prevent the recurrence of such a disease or to promote immunity against such a disease. The amount is preferably about 0.5 percent to about 9 percent by weight based on the total weight of a formulation.

5 A fatty acid such as isostearic acid, oleic acid or a mixture thereof is incorporated into a formulation of the invention. The total amount of fatty acid present in a formulation is preferably about 3 percent to about 45 percent by weight based on the total weight of a formulation.

10 A pharmaceutical formulation of the invention can be in a form such as a cream, an ointment, a pressure-sensitive adhesive composition, or other forms known to those skilled in the art, each particular form containing 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine and fatty acid in particular amounts, and optionally containing various additional elements. The preferred amounts of drug and fatty acid, and the amounts and types of optional elements used in formulations of the invention are discussed below with particular reference to creams, ointments, and adhesive compositions.

15 A cream according to the invention contains 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine and fatty acid.

16 The amount of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine present in a cream is preferably about 0.5 percent to about 9 percent by weight, and more preferably about 1 percent to about 5 percent by weight, based on the total weight of the cream.

20 The total amount of fatty acid present in a cream of the invention is preferably about 3 percent to about 45 percent by weight, and more preferably about 5 percent to about 25 percent by weight, based on the total weight of the cream.

25 Optionally, a cream of the invention can contain emollients, emulsifiers, thickeners, and/or preservatives.

Emollients such as long chain alcohols, e.g., cetyl alcohol, stearyl alcohol and cetearyl alcohol; hydrocarbons such as petrolatum and light mineral oil; or acetylated lanolin can be included in a cream of the invention. A cream can contain one or more of these emollients. The total amount of emollient in a 30 cream of the invention is preferably about 5 percent to about 30 percent, and more preferably about 5 percent to about 10 percent by weight based on the total weight of the cream.

35 Emulsifiers such as nonionic surface active agents, e.g., polysorbate 60 (available from ICI Americas), sorbitan monostearate, polyglyceryl-4 oleate, and polyoxyethylene(4)lauryl ether or trivalent cationic emulsifiers such as aluminum stearate can be included in a cream of the invention. A cream can contain one or more emulsifiers. Generally the total amount of emulsifier is preferably about 2 percent to about 14 percent, and more preferably about 2 percent to about 6 percent by weight based on the total weight of the cream.

40 Pharmaceutically acceptable thickeners, such as VeegumTMK (available from R. T. Vanderbilt Company, Inc.), and long chain alcohols (i.e. cetyl alcohol, stearyl alcohol or cetearyl alcohol) can be used. A cream can contain one or more thickeners. The total amount of thickener present is preferably about 3 percent to about 12 percent by weight based on the total weight of the cream.

45 Preservatives such as methylparaben, propylparaben and benzyl alcohol can be present in a cream of the invention. The appropriate amount of such preservative(s) is known to those skilled in the art.

50 Optionally, an additional solubilizing agent such as benzyl alcohol, lactic acid, acetic acid, stearic acid or hydrochloric acid can be included in a cream of the invention. If an additional solubilizing agent is used, the amount present is preferably about 1 percent to about 12 percent by weight based on the total weight of the cream.

55 Optionally, a cream of the invention can contain a humectant such as glycerin, skin penetration enhancers such as butyl stearate, and additional solubilizing agents.

It is known to those skilled in the art that a single ingredient can perform more than one function in a cream, i.e., cetyl alcohol can serve both as an emollient and as a thickener.

Generally, a cream consists of an oil phase and a water phase mixed together to form an emulsion. Preferably, the amount of water present in a cream of the invention is about 45 percent to about 85 percent by weight based on the total weight of the cream.

The oil phase of a cream of the invention can be prepared by first combining the 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine and the fatty acid (if the cream contains benzyl alcohol it can also be added at this point) and heating with occasional stirring to a temperature of about 50 °C to 85 °C. When the 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine appears to be completely dissolved, the remaining oil phase ingredients are added and heating is continued until dissolution appears to be complete.

The water phase can be prepared by combining all other ingredients and heating with stirring until dissolution appears to be complete.

The creams of the invention are generally prepared by adding the water phase to the oil phase with both phases at a temperature of about 65 °C to 75 °C. The resulting emulsion is mixed with a suitable mixer apparatus to give the desired cream.

An ointment of the invention contains an ointment base in addition to 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine and fatty acid.

The amount of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine present in an ointment of the invention is preferably about 0.5 percent to about 9 percent, and more preferably about 0.5 percent to about 5 percent by weight based on the total weight of the ointment.

The total amount of fatty acid present in an ointment of the invention is preferably about 3 percent to about 45 percent, and more preferably about 3 percent to about 25 percent based on the total weight of the ointment.

A pharmaceutically acceptable ointment base such as petrolatum or polyethylene glycol 400 (available from Union Carbide) in combination with polyethylene glycol 3350 (available from Union Carbide) can be used. The amount of ointment base present in an ointment of the invention is preferably about 60 percent to about 95 percent by weight based on the total weight of ointment.

Optionally, an ointment of the invention can also contain emollients, emulsifiers and thickeners. The emollients, emulsifiers, and thickeners and the preferred amounts thereof described above in connection with creams are also generally suitable for use in an ointment of the invention.

An ointment according to the invention can be prepared by combining 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine with fatty acid and heating with occasional stirring to a temperature of about 65 °C. When the 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine appears to be completely dissolved, the remaining ingredients are added and heated to about 65 °C. The resulting mixture is mixed with a suitable mixer while being allowed to cool to room temperature.

A pressure-sensitive adhesive composition of the invention contains 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, fatty acid, and a pressure sensitive adhesive polymer.

The amount of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine present in a pressure sensitive adhesive composition of the invention is preferably about 0.5 percent to about 9 percent by weight, and more preferably about 3 percent to about 7 percent by weight based on the total weight of the adhesive composition. The amount of fatty acid present is preferably about 10 percent to about 40 percent by weight, more preferably about 15 percent to about 30 percent by weight, and most preferably about 20 percent to about 30 percent by weight, based on the total weight of the adhesive composition.

Preferably, the adhesive polymer utilized in a pressure sensitive adhesive composition of the invention is substantially chemically inert to 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine. The adhesive polymer is preferably present in an amount of about 55 percent to about 85 percent by weight based on the total weight of the composition. Suitable adhesive polymers include acrylic adhesives that contain, as a major constituent (i.e., at least about 80 percent by weight of all monomers in the polymer), a hydrophobic monomeric acrylic or methacrylic acid ester of an alkyl alcohol, the alkyl alcohol containing 4 to 10 carbon atoms. Examples of suitable monomers are those discussed below in connection with the "A Monomer". These adhesive polymers can further contain minor amounts of other monomers such as the "B Monomers" listed below.

Preferred adhesives include acrylic pressure-sensitive adhesive copolymers containing A and B Monomers as follows: Monomer A is a hydrophobic monomeric acrylic or methacrylic acid ester of an alkyl alcohol, the alkyl alcohol containing 4 to 10 carbon atoms, preferably 6 to 10 carbon atoms, more preferably 6 to 8 carbon atoms, and most preferably 8 carbon atoms. Examples of suitable A Monomers are n-butyl, n-pentyl, n-hexyl, isoheptyl, n-nonyl, n-decyl, isohexyl, 2-ethyloctyl, isoocetyl and 2-ethylhexyl acrylates. The most preferred A Monomer is isoocetyl acrylate.

Monomer B is a reinforcing monomer selected from the group consisting of acrylic acid; methacrylic acid; alkyl acrylates and methacrylates containing 1 to 3 carbon atoms in the alkyl group; acrylamide; methacrylamide; lower alkyl-substituted acrylamides (i.e., the alkyl group containing 1 to 4 carbon atoms) such as tertiary-butyl acrylamide; diacetone acrylamide; n-vinyl-2-pyrrolidone; vinyl ethers such as vinyl tertiary-butyl ether; substituted ethylenes such as derivatives of maleic anhydride, dimethyl itaconate and monoethyl formate and vinyl perfluoro-n-butyrate. The preferred B Monomers are acrylic acid, methacrylic acid, the above-described alkyl acrylates and methacrylates, acrylamide, methacrylamide, and the above-described lower alkyl substituted acrylamides. The most preferred B Monomer is acrylamide.

In one embodiment of a pressure-sensitive adhesive composition of the invention, the pressure-sensitive adhesive copolymer containing A and B Monomers as set forth above preferably contains the A Monomer in an amount by weight of about 80 percent to about 98 percent of the total weight of all monomers in the copolymer. The A Monomer is more preferably present in an amount by weight of about 88 percent to about 98 percent, and is most preferably present in an amount by weight of about 91 percent to about 98 percent. The B Monomer in such a copolymer is preferably present in the pressure-sensitive adhesive copolymer in an amount by weight of about 2 percent to about 20 percent, more preferably about

2 percent to about 12 percent, and most preferably 2 to 9 percent of the total weight of the monomers in the copolymer.

In another embodiment of a pressure-sensitive adhesive composition of the invention, the adhesive copolymer comprises about 60 to about 80 percent by weight (and preferably about 70 to about 80 percent by weight) of the above-mentioned hydrophobic monomeric acrylic or methacrylic acid ester of an alkyl alcohol (i.e., Monomer A described above) based on the weight of all monomers in the copolymer; about 4 to about 9 percent by weight based on the weight of all monomers in the copolymer of a reinforcing monomer selected from the group consisting of acrylic acid, methacrylic acid, an alkyl acrylate or methacrylate containing 1 to 3 carbon atoms in the alkyl group, acrylamide, methacrylamide, a lower alkyl-substituted acrylamide, diacetone acrylamide and N-vinyl-2-pyrrolidone; and about 15 to about 35 percent by weight (and preferably about 15 to about 25 percent by weight) of vinyl acetate based on the weight of all monomers in the copolymer. In this embodiment the preferred acrylic or methacrylic acid ester is isoctyl acrylate and the preferred reinforcing monomer is acrylamide.

The above described adhesive copolymers are known, and methods of preparation therefor are well known to those skilled in the art, having been described for example, in U.S. Patent RE 24,906 (Ulrich). The polymerization reaction can be carried out using a free radical initiator such as an organic peroxide (e.g., benzoylperoxide) or an organic azo compound (e.g., 2,2'-azobis(2,4-dimethylpentanenitrile) available under the trade designation "Vazo 52" from DuPont).

Since pressure-sensitive adhesives such as those described above are inherently rubbery and tacky and are suitably heat and light stable, there is no need to add tackifiers or stabilizers. However, such can be added if desired.

Optionally, a pressure sensitive adhesive composition of the invention can also contain one or more skin penetration enhancers such as glyceryl monolaurate, ethyl oleate, isopropyl myristate, diisopropyl adipate and N,N-dimethyldodecylamine-N-oxide, either as a single ingredient or as a combination of two or more ingredients. The skin penetration enhancer(s) preferably form a substantially homogeneous mixture with the pressure sensitive adhesive polymer or copolymer. The total amount of skin penetration enhancer(s) present in a pressure sensitive adhesive composition of the invention is preferably about 3 percent to about 25 percent by weight, more preferably about 3 percent to about 10 percent by weight based on the total weight of the adhesive composition.

When the skin penetration enhancer is a single ingredient, it is preferably a skin penetration enhancer such as isopropyl myristate, diisopropyl adipate, ethyl oleate, or glyceryl monolaurate.

When a combination skin penetration enhancer is used, it is preferably a combination such as: ethyl oleate with glyceryl monolaurate; ethyl oleate with N,N-dimethyldodecylamine-N-oxide; glyceryl monolaurate with N,N-dimethyldodecylamine-N-oxide; and ethyl oleate with both glyceryl monolaurate and N,N-dimethyldodecylamine-N-oxide.

A pressure-sensitive adhesive composition of the invention can be prepared by combining dry adhesive, 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, fatty acid, and skin penetration enhancer(s) with an organic solvent. The preferred organic solvents are methanol and ethyl acetate. The total solids content of the adhesive coating is preferably in the range of about 15 percent to about 40 percent, and more preferably in the range of about 20 to about 35 percent based on the total weight of the adhesive coating. The resulting mixture is shaken or mixed for a period of about 20 to 72 hours. When this method is used it is preferred that the 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine be in micronized form (i.e., particle size of 1-2 microns in diameter). Optionally, the mixture can be heated during shaking.

In a preferred method, the 1-isobutyl-1H-imidazo-[4,5-c]quinolin-4-amine is combined with the fatty acid and shaken at 40 °C until there appears to be complete dissolution. The remaining ingredients are added and the mixture is shaken for a period of about 20 to 72 hours.

The pressure-sensitive adhesive compositions described above are preferably coated onto one surface of a suitable backing of sheet material, such as a film, to form a pressure-sensitive adhesive coated sheet material. A pressure-sensitive adhesive coated sheet material of the invention can be prepared by knife coating a suitable release liner to a predetermined uniform thickness with a wet adhesive formulation. This adhesive coated release liner is then dried and laminated onto a backing using conventional methods. Suitable release liners include conventional release liners comprising a known sheet material, such as a polyester web, a polyethylene web, or a polystyrene web, or polyethylene-coated paper, coated with a suitable silicone-type coating such as that available under the trade designation Daubert 164Z, from Daubert Co. The backing can be occlusive, non-occlusive or a breathable film as desired. The backing can be any of the conventional materials for pressure-sensitive adhesive tapes, such as polyethylene, particularly low density polyethylene, linear low density polyethylene, high density polyethylene, randomly-oriented nylon fibers, polypropylene, ethylene-vinylacetate copolymer, polyurethane, rayon and the like. Backings that are

layered, such as polyethylene-aluminum-polyethylene composites are also suitable. The backing should be substantially non-reactive with the ingredients of the adhesive coating. The presently preferred backing is low density polyethylene.

The pressure-sensitive adhesive coated sheet material of the invention can be made in the form of an article such as a tape, a patch, a sheet, a dressing or any other form known to those skilled in the art.

Preferably, an article in the form of a patch is made from an adhesive coated sheet material of the invention and applied to the skin of a mammal. The patch is replaced as necessary with a fresh patch to maintain the particular desired therapeutic effect of the 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine.

The following test methods have been employed in the examples which thereafter follow.

10

In Vitro Test Method

15 Although animal skins are known to give significant quantitative differences in drug penetrability as compared to human skin, a rank order correlation is generally observed with various drugs (M. J. Bartek and J. A. LaBudde in "Animal Modes in Dermatology", H. Maibach, Ed., Churchill Livingstone, New York, 1975, pp. 103-119). Hairless mouse skin has been recommended as a readily available animal skin for use in diffusion cells with steroids and other small molecules (R. B. Stoughton, Arch. Derm., 99, 753 (1969), J. 20 L. Cohen and R. B. Stoughton, J. Invest. Derm. 62, 507 (1974), R. B. Stoughton in "Animal Modes in Dermatology", pp. 121-131). In the specific test procedure used herein, hairless mouse skin removed from female hairless mice that were 40-80 days old (available from Jackson Laboratory, Strain HRS/J) was used. The skin was maintained on ice until use, and it was preferably used within 8 hours of sacrifice. The mouse skin was mounted on a diffusion cell of the type shown in the Drawing. The cell is modeled after those 25 described in the literature, e.g., J. L. Cohen, R. B. Stoughton, J. Invest. Derm., 62, 507 (1974) and R. B. Stoughton, Arch. Derm., 99, 753 (1964). As shown in the Drawing, the mouse skin 20 was mounted epidermal side up between upper and lower portions of the cell 21 and 22, which are held together by means of a ball joint clamp 23.

30 The portion of the cell below the mounted skin was completely filled with 0.1 N hydrochloric acid such that the receptor fluid contacted the skin. The receptor fluid was stirred using a magnetic stir bar 24 and a magnetic stirrer (not illustrated). The sampling port 25 was covered with a material such as Parafilm^R except when in use.

35 When a cream or ointment was evaluated, approximately 100 mg of the formulation was applied to the epidermal (upper) side of the skin to cover in an even layer only the area of the skin that would be in contact with the receptor fluid when the skin is mounted in the diffusion cell. When an adhesive coated sheet material was evaluated, the skin was mounted on the diffusion cell and a 2.056 cm² patch was applied to the skin and pressed to cause uniform contact to the skin. Generally, the cream or the patch was applied to the skin prior to the time the receptor fluid was added to the cell below the skin.

40 The cell was then placed in a constant temperature ($32 \pm 2^\circ\text{C}$) chamber. To maintain constant temperature, the chamber utilized a heat exchanger coupled to a constant temperature bath, with a fan to circulate air. The receptor fluid was stirred by means of a magnetic stirring bar throughout the experiment to assure a uniform sample and a reduced diffusion barrier layer on the dermal side of the skin. A sample of receptor fluid was removed at specified times. The withdrawn receptor fluid was analyzed for drug content by conventional high pressure liquid chromatography as follows:

45 A 15 centimeter column containing Zorbax^{TMC₈} (an octylsilane, available from E. I. Dupont de Nemours & Company), 5 micron particle size, was used. The mobile phase was 35 percent acetonitrile/65 percent water (volume/volume) containing 0.2 percent tetramethylammonium hydroxide and 0.2 percent 1-dodecanesulfonate sodium, with the pH of the mobile phase adjusted to 2.0 with phosphoric acid. The flow rate was 2 ml per minute. Ultraviolet detection at 254 nanometers was used. The amount of drug 50 penetrating the skin over the specified time period was calculated as a percentage of the dose applied to the skin.

This in vitro method is referred to as the hairless mouse skin model in the claims. For purposes of the claims where this model is referred to the values stated for skin penetration are the average of 4 independent determinations using a different mouse skin for each determination.

55

In Vivo Test Method

Formulations of the invention can also be evaluated in vivo for their ability to inhibit lesion formation in guinea pigs infected with Herpes simplex virus Type II and for their ability to induce interferon production in guinea pigs.

In the specific test method used herein, care was taken to be sure the formulation had optimal penetration by washing the backs of the guinea pigs with mild detergent before the formulations were applied. One treatment was given at 24 hours preinfection. When a cream or ointment was evaluated, 200 microliters of the formulation was applied topically to the back of the guinea pig, rubbed in, covered with a Hill-top Chamber and then wrapped with MediporeTM brand tape (commercially available from 3M). When an adhesive coated sheet material was evaluated, an article in the form of a patch of a specified size was applied to the back of the guinea pig and wrapped with MediporeTM brand tape. After the patch had been in place for 24 hours, it was removed and the guinea pig was infected with the virus as described below.

Female Hartley guinea pigs (150-200 grams) were abraded in the vaginal area with a dry cotton swab. The guinea pigs were then infected intravaginally with a cotton swab saturated with HSV-2 (1×10^{-5} plaque forming units/ml). The formulations of the invention were evaluated by comparing lesion development in treated and untreated animals. External lesions were scored daily for ten days, unless otherwise specified, using the following scale: 0, no lesion; 1, redness and swelling; 2, a few small vesicles; 3, several large vesicles; 4, large ulcers and necrosis; 5, paralysis. The percent Lesion Inhibition was calculated as follows: $100 - [(Sum \text{ of } maximum \text{ lesion } scores \text{ of } treated \text{ group } divided \text{ by } the \text{ Sum } of \text{ the } maximum \text{ scores } of \text{ infected } control) \times 100]$.

Interferon levels in the guinea pigs was monitored by bleeding via cardiac puncture of anesthetized guinea pigs 17 to 24 hours after dosing. The serum of each animal was separately assayed for interferon activity as follows:

The serum was diluted and incubated with guinea pig fibroblast cells at 37 °C overnight in 96 well microtiter plates. The incubated cells were then challenged with an inoculum of mengovirus that is sufficient to kill untreated cells in two days. Two days after such a challenge, the cells were examined both microscopically and after staining with crystal violet to determine whether the cells remain intact. The results were reported as activity/ml. Activity/ml indicates the highest dilution of serum that protects cells from virus challenge. An untreated guinea pig control typically exhibits an activity/ml of less than about 100, although activity/ml has been observed to exceed 100.

30

Inherent Viscosity Measurement

35 The inherent viscosity values reported in the Examples below were obtained by the conventional method used by those skilled in the art. The measurement of the viscosity of dilute solutions of the adhesive, when compared to controls run under the same conditions, clearly demonstrates the relative molecular weights. It is the comparative values that are significant; absolute figures are not required. In the examples, the inherent viscosity values were obtained using a Cannon-Fenske #50 viscometer to measure 40 the flow time of 10 ml of a polymer solution (0.2 g polymer/deciliter tetrahydrofuran, in a water bath controlled at 25 °C). The examples and the controls were run under identical conditions. The test procedure followed and the apparatus used are explained in detail in the Textbook of Polymer Science, F. W. Billmeyer, Wiley-Interscience, 2nd Edition, 1971 under: Polymer chains and their characterization, D. Solution Viscosity and Molecular Size, pp 84-85.

45 The following examples are provided to illustrate the invention, but are not intended to be limiting thereof. Parts and percentages are by weight unless otherwise specified.

PREPARATIVE METHOD 1

50

Laboratory Scale Preparation of Isooctylacrylate/Acrylamide Copolymer

55 To a 114 gram narrow-mouth glass bottle were added: 18.6 g isooctyl acrylate, 1.4 g acrylamide, 0.04 g benzoyl peroxide, 27.0 g ethyl acetate and 3.0 g methanol. The solution was purged for thirty five seconds with nitrogen at a flow rate of one liter per minute. The bottle was sealed and placed in a rotating water bath

at 55 °C for twenty-four hours to effect essentially complete polymerization. The polymer was diluted with ethyl acetate/methanol (90/10) to 23.2 percent solids and had a measured inherent viscosity of 1.26 dl/g in ethyl acetate.

5

PREPARATIVE METHOD 2

10

Pilot Plant Scale Preparation of Isooctylacrylate/Acrylamide Copolymer

155 kg isooctylacrylate, 11.6 kg acrylamide, 209.1 kg ethyl acetate and 23.2 kg methanol were charged to a clean, dry reactor. Medium agitation was applied. The batch was deoxygenated with nitrogen while heating to an induction temperature of 55 °C. 114 g LucidoITM70 initiator (available from Pennwalt Corp.) mixed with 2.3 kg ethyl acetate was charged to the reactor. The temperature was maintained at 55 °C throughout the reaction. After 5.5 hours reaction time, 114 g LucidoITM70 mixed with 2.3 kg ethyl acetate were charged to the reactor. After 9.0 hours reaction time, an additional 114 g LucidoITM70 initiator mixed with 2.3 kg ethyl acetate were charged to the reactor. The reaction was continued until the percent conversion was greater than 98 percent as measured by gas chromatographic evaluation of residual monomer concentration. The resulting polymer solution was diluted to 25-28 percent solids with ethyl acetate/methanol (90/10) and had a measured Brookfield viscosity of 17,000-21,000 centipoises using spindle #4 at 12 rpm. The polymer had a measured inherent viscosity of 1.3-1.4 dl/g in ethyl acetate.

20 The above procedure was found to provide a pressure-sensitive adhesive that is equivalent in the practice of the present invention to a pressure-sensitive adhesive prepared according to PREPARATIVE METHOD 1.

25 A 25-30 percent solids solution of the isooctyl acrylate:acrylamide (93:7) adhesive copolymer in ethyl acetate/methanol (90:10) was coated onto a two-sided release liner using a knife-coater and coating at 0.5 mm in thickness. The adhesive-coated laminate was dried first at 82 °C for 3 minutes and then at 116 °C for 30 3 minutes. The dried adhesive coating was then stripped off the release liner and placed in a glass bottle. The foregoing procedure results in a reduction of the amount of any residual monomer in the adhesive copolymer.

35

PREPARATIVE METHOD 3

40

Preparation of Isooctyl Acrylate: Acrylamide: Vinyl Acetate (75:5:20) Copolymer

45

The procedure of PREPARATIVE METHOD 1 above was repeated this time employing 120.0 g isooctyl acrylate, 8.0 g acrylamide, 32.0 g vinyl acetate, 0.32 g benzoyl peroxide, 216.0 g ethyl acetate and 24.0 g methyl alcohol. The resulting polymer was diluted with the ethyl acetate/methyl alcohol mixture to 21.52% solids. The adhesive polymer had a measured inherent viscosity of 1.40 dl/g in ethyl acetate at a concentration of 0.15 g/dl. Its Brookfield viscosity was 2,300 centipoise.

50

PREPARATIVE METHOD 4

55

Preparation of Isooctyl Acrylate: Acrylamide: Vinyl Acetate (75:5:20) Copolymer

55

A master batch was prepared by combining 621.0 g of isooctyl acrylate, 41.4 g of acrylamide, 165.6 g of vinyl acetate, 1.656 g of 2,2'-azobis(2,4-dimethylpentanenitrile) (available from the Dupont Company as VazoTM52), 884.52 g of ethyl acetate and 87.48 g of methanol. A 400 g portion of the resulting solution was

placed in an amber quart bottle. The bottle was purged for two minutes with nitrogen at a flow rate of one liter per minute. The bottle was sealed and placed in a rotating water bath at 45 ° C for twenty-four hours to effect essentially complete polymerization. The copolymer was diluted with 250 g of ethyl acetate/methanol (90/10) to 26.05% solids and had a measured inherent viscosity of 1.27 dl/g in ethyl acetate at a concentration of 0.15 g/dl. Its Brookfield viscosity was 5580 centipoise.

EXAMPLE 1

10

A cream according to the present invention was prepared from the following ingredients:

Oil Phase	% by Weight	Amount
1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine	1.0	40.0 g
Isostearic acid	10.0	400.0 g
Benzyl alcohol	2.0	80.0 g
Cetyl alcohol	2.2	88.0 g
Stearyl alcohol	3.1	124.0 g
Polysorbate 60	2.55	102.0 g
Sorbitan monostearate	0.45	18.0 g
Aqueous Phase		
Glycerin	2.0	80.0 g
Methylparaben	0.2	8.0 g
Propylparaben	0.02	0.8 g
Purified water	76.48	3059.2 g

30

The materials listed above were combined according to the following procedure:

The glycerin, methylparaben, propylparaben and water were weighed into a 4 liter glass beaker then heated on a hot plate with stirring until the parabens were in solution (the temperature reached 80 ° C). The isostearic acid and 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine were weighed into an 8 liter stainless steel beaker and heated on a hot plate until the amine was in solution (the temperature reached 69 ° C). The benzyl alcohol, cetyl alcohol, stearyl alcohol, polysorbate 60 and sorbitan monostearate were added to the isostearic acid solution and heated on a hot plate until all material was dissolved (the temperature reached 75 ° C). With both phases at approximately the same temperature (65-75 ° C), the water phase was added to the oil phase. The mixture was mixed with a homogenizer for 13 minutes then put into a cool water bath and mixed with a 3 inch propeller for 40 minutes (the temperature was 29 ° C). The resulting cream was placed in glass jars.

EXAMPLES 2-9

45

Using the general method of Example 1, the cream formulations shown in Tables 1 and 2 were prepared.

50

55

TABLE 1

		% by Weight			
		Example			
5 10 15 20 25	Oil Phase	2	3	4	5
	1-Isobutyl-1H-imidazo-[4,5-c]quinolin-4-amine	1.0	1.0	1.0	1.0
	Isostearic acid	10.0	10.0	5.0	5.0
	Benzyl alcohol	-	2.0	-	-
	Cetyl alcohol	-	1.7	-	-
	Stearyl alcohol	-	2.3	-	-
	Cetearyl alcohol	6.0	-	6.0	6.0
	Polysorbate 60	2.55	2.55	2.55	2.55
	Sorbitan monostearate	0.45	0.45	0.45	0.45
	BrijTM30 ^a	-	-	-	10.0
Aqueous Phase					
Glycerin		2.0	2.0	2.0	2.0
Methylparaben		0.2	0.2	0.2	0.2
Propylparaben		0.02	0.02	0.02	0.02
Purified water		77.78	77.78	82.78	72.78

BrijTM30 (polyoxyethylene(4) lauryl ether) is available from ICI Americas, Inc.

TABLE 2

30 35 40 45 50		% by Weight			
		Example			
		6	7	8	9
Oil Phase	1-Isobutyl-1H-imidazo-[4,5-c]quinolin-4-amine	1.0	1.0	1.0	1.0
	Isostearic acid	10.0	25.0	10.0	6.0
	Benzyl alcohol	-	2.0	-	2.0
	Cetyl alcohol	-	2.2	1.7	-
	Stearyl alcohol	-	3.1	2.3	-
	Cetearyl alcohol	6.0	-	-	6.0
	Polysorbate 60	2.55	3.4	2.55	2.55
	Sorbitan monostearate	0.45	0.6	0.45	0.45
	BrijTM30	10.0	-	-	-
	Aqueous Phase	2.0	2.0	2.0	2.0
Glycerin		0.2	0.2	0.2	0.2
Methylparaben		0.02	0.02	0.02	0.02
Propylparaben		67.78	60.48	79.78	79.78

A cream according to the present invention was prepared from the following ingredients:

	Oil Phase	% by Weight	Amount
5	1-Isobutyl-1H-imidazo[4,5-c]quinolin-4-amine	1.0	3.00 g
	Isostearic acid	5.0	15.0 g
	White petrolatum	15.0	45.0 g
	Light mineral oil	12.8	38.4 g
	Aluminum stearate	8.0	24.0 g
	Cetyl alcohol	4.0	12.0 g
	WitconolTM14 ^a	3.0	9.00 g
	Acetylated lanolin	1.0	3.0 g
	Propylparaben	0.063	0.19 g
10	Aqueous Phase		
	VeegumTMK ^b	1.0	3.0 g
	Methylparaben	0.12	0.36 g
15	Purified water	49.017	147.05 g

^aWitconolTM14 (polyglyceryl-4 oleate) is available from Witco Chemical Corp.

Organics Division

^b VeegumTMK (colloidal magnesium aluminum silicate) is available from R. T. Vanderbilt Company Inc.

25

The materials listed above were combined according to the following procedure:

The 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine and the isostearic acid were weighed into a glass jar and heated with occasional stirring until the amine was dissolved (the temperature reached 68 °C). To this solution was added, the petrolatum, mineral oil, aluminum stearate, cetyl alcohol, WitconolTM14, acetylated lanolin and propylparaben. The mixture was heated to 75 °C. In a separate beaker, the methylparaben and water were combined and heated until the paraben dissolved (the temperature reached 61 °C). The VeegumTMK was added to the aqueous solution and heated at 75 °C for 30 minutes while mixing with a homogenizer. With both phases at 75 °C, the aqueous phase was slowly added to the oil phase while mixing with a homogenizer. Mixing was continued for 30 minutes while maintaining a temperature of about 80 °C. The jar was then capped and the formulation was allowed to cool.

EXAMPLE 11

40

An ointment according to the present invention was prepared from the following ingredients:

		% by Weight	Amount
45	1-Isobutyl-1H-imidazo[4,5-c]quinolin-4-amine	1.0	0.20 g
	Isostearic acid	5.0	1.00 g
	Mineral oil	12.8	2.56 g
	White petrolatum	65.2	13.04 g
	Cetyl alcohol	4.0	0.80 g
	Acetylated lanolin	1.0	0.20 g
	WitconolTM14	3.0	0.60 g
	Aluminum stearate	8.0	1.60 g

55

The materials listed above were combined according to following procedure:

The 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine and the isostearic acid were placed in a glass jar and

heated with stirring until the amine was dissolved. The remaining ingredients were added and the resulting mixture was heated to 65 °C and then mixed while being allowed to cool to room temperature.

5

EXAMPLE 12

Using the general procedure of Example 11 an ointment containing the following ingredients was prepared.

10

15

		% by Weight	Amount
	1-Isobutyl-1H-imidazo[4,5-c]quinolin-4-amine	1.0	0.20 g
	Isostearic acid	6.0	1.20 g
	Polyethylene Glycol 400	55.8	11.16 g
	Polyethylene Glycol 3350	32.6	6.52 g
	Stearyl alcohol	4.6	0.92 g

20

EXAMPLES 13-15

25

Creams of the present invention were prepared using the ingredients shown in Table 3. The formulations were prepared using the general method of Example 1 except that benzyl alcohol was used with the isostearic acid to dissolve the 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine.

30

TABLE 3

35

40

45

50

55

		Example		
		13	14	15
		% by Weight		
	Oil Phase			
	1-Isobutyl-1H-imidazo[4,5-c]quinolin-4-amine	5.0	5.0	4.85
	Isostearic acid	25.0	25.0	24.3
	Benzyl alcohol	2.0	2.0	1.94
	Cetyl alcohol	2.2	2.2	1.16
	Stearyl alcohol	3.1	3.1	1.75
	Petrolatum	3.0	-	2.91
	Polysorbate 60	3.4	3.4	4.13
	Sorbitan monostearate	0.6	0.6	0.73
	Stearic acid	-	-	9.71
	Aqueous Phase			
	Glycerin	2.0	2.0	1.94
	Methylparaben	0.2	0.2	0.19
	Propylparaben	0.02	0.02	0.02
	Purified water	53.48	56.48	46.39

EXAMPLE 16

A cream according to the present invention was prepared from the following ingredients:

	Oil Phase	% by Weight	Amount
5	1-Isobutyl-1H-imidazo[4,5-c]quinolin-4-amine	4.0	0.80 g
	Isostearic acid	20.0	4.00 g
	Benzyl alcohol	2.0	0.40 g
	Cetyl alcohol	2.2	0.49 g
	Stearyl alcohol	3.1	0.62 g
	Polysorbate 60	3.4	0.68 g
	Sorbitan monostearate	0.6	0.12 g
10	Aqueous Phase		
	1-Isobutyl-1H-imidazo[4,5-c]quinolin-4-amine	1.0	0.2 g
	Glycerin	2.0	0.4 g
	85% Lactic acid	1.0	0.22 g
	Methylparaben	0.2	0.04 g
	Propylparaben	0.02	0.004 g
	Purified water	60.48	12.0 g

25 The materials listed above were combined according to the following procedure:
The isostearic acid and 0.8 g of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine were combined in a glass jar and heated with stirring until the amine had dissolved. The remaining oil phase ingredients were added to this solution and the mixture was heated to about 70 °C. The aqueous phase ingredients were weighed into a separate beaker and heated with stirring until the amine and the parabens had dissolved. With both 30 phases at about 70 °C, the water phase was added to the oil phase and mixed with a propeller until the mixture cooled to room temperature.

EXAMPLE 17

The formulations of Examples 1-16 of the invention were tested in the hairless mouse skin model described above. The results are summarized in Table 4.

40

45

50

55

TABLE 4

Formulation	Number of Determinations	Average % Penetration in 24 Hours
Example 1	8 ^a	21.1 ± 7.2
Example 2	16 ^a	14.7 ± 4.2
Example 3	4	19.5 ± 3.9
Example 4	12 ^a	14.3 ± 3.6
Example 5	4	17.2 ± 2.0
Example 6	4	36.8 ± 4.3
Example 7	4	37.5 ± 13.1
Example 8	4	18.8 ± 2.0
Example 9	4	22.4 ± 4.8
Example 10	8 ^a	32.7 ± 4.1
Example 11	4	21.6 ± 1.4
Example 12	4	14.3 ± 0.6
Example 13	4	58.6 ± 9.2
Example 14	8 ^a	39.6 ± 7.4
Example 15	4	28.9 ± 4.2
Example 16	8 ^a	33.0 ± 9.6

^a The determinations were run on different days in groups of 4.

As shown above, the formulations of the invention provide for significant penetration of the active agent. Several formulations of the present invention were tested in the guinea pig model described above. The results are shown in Table 5.

TABLE 5

Formulation	Percent Lesion Inhibition	Interferon level (activity/ml)
Example 1	95	> 12,800
Example 2 ^a	43	1,333
Example 2 ^a	40	5,066
Example 6	29	2,133
Example 10	30	1,866
Example 13	60	1,200
Example 16	50	5,800

^a The formulation of Example 2 was tested on two separate occasions.

The formulation of Example 1 was again run in the intravaginal guinea pig model. The protocol was as described above except that the animals were treated twice daily for 4 days starting 6 hours after infection. The results are summarized in Table 6.

TABLE 6

Level	Formulation	Percent Lesion Inhibition	Interferon (activity/ml)
Example 1		71	1200

EXAMPLE 18

A mixture of 5.9415 g of the 93:7 isoctyl acrylate:acrylamide adhesive copolymer prepared in PREPARATIVE METHOD 2 above, 1.5126 g isostearic acid, 2.0075 g ethyl oleate, 0.3021 g glycetyl monolaurate, 0.2936 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine (micronized) and 23.7 g of 90:10 ethyl acetate:methanol was placed in a small glass jar. The jar was placed on a horizontal shaker and shaken at room temperature for about 13 hours. The formulation was coated at a thickness of 20 mils onto a 5 mil Daubert 164Z liner. The laminate was oven dried for 3 minutes at 105° F, for 2 minutes at 185° F, and for 2 minutes at 210° F. The resulting adhesive coating contained 59.1 percent 93:7 isoctyl acrylate:acrylamide adhesive copolymer, 15.0 percent isostearic acid, 20.0 percent ethyl oleate, 3.0 percent glycetyl monolaurate and 2.9 percent 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine. The material was then laminated with 3 mil low density polyethylene backing and die cut into 2.056 cm² patches. Penetration through hairless mouse skin was measured using the diffusion apparatus and method described above. Three independent determinations were carried out. The average penetration in 24 hours was 46.5% of the applied dose.

EXAMPLE 19 and COMPARATIVE EXAMPLE 20

Using the method described in Example 18, the formulations shown below were prepared and the penetration through hairless mouse skin measured. The adhesive used was a copolymer of isoctyl acrylate:acrylic acid (94:6) and had an inherent viscosity of 1.45-1.60 dl/g in ethyl acetate. The solvent used was heptane:isopropanol (70:30). Patches that measured 2.056 cm² were employed. Three independent determinations were carried out and the results were averaged.

Formulation	Average Percent Penetration in 24 hours
Example 19 3.0% 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine (micronized) 15% Isostearic acid 82% adhesive	20.5 ± 6.4
Comparative Example 20 3.1% 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine (micronized) 96.9% adhesive	4.0 ± 1.5

This example shows that a pressure-sensitive adhesive coated sheet material of the invention exhibits superior penetration of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine as compared to one not containing a fatty acid.

EXAMPLES 21 - 45

Using the method described in Example 18, the formulations shown in Table 7 below were prepared and the penetration through hairless mouse skin was measured. The adhesive used was the copolymer of isoctyl acrylate:acrylamide (93:7), prepared in PREPARATIVE METHOD 1 above. The solvent was 90:10 ethyl acetate:methanol. The 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine used was micronized. All formulations were mixed at room temperature unless otherwise indicated. Patches that measured 2.056 cm² were used and four independent determinations were carried out for each formulation unless otherwise indicated and the results were averaged.

50
55
45
40
35
30
25
20
15
10
5
0**TABLE 7**

EXAMPLE	% BY Weight						HMS
	ADHESIVE	AMINE	ISO	OLEIC	EO	GML	
21	82.1	2.9	15.0				22.5* ± 1.76
22*	78.8	3.0	15.0		3.2		32.4 ± 1.44
23*	72.0	3.0	15.0		10.0		33.8 ± 2.62
24*	75.5	3.0	15.0		5.0	1.5	33.3 ± 2.17
25*	71.9	3.0			51.9	10.0	39.9 ± 5.73
26*	76.9	3.0			20.1		42.2 ± 1.68
27	68.3	3.0	6.0	9.1	12.1	1.5	33.8 ± 5.38
28	69.7	3.0	6.0	9.1	12.1		26.5 ± 2.61
29	70.0	3.0	6.0	13.0	8.0		44.3 ± 7.69
30	66.9	3.0			20.0	10.1	33.2 ± 7.78
31	72.0	3.0	15.0				10.0 ^c
32	71.9	3.0			15.0		10.1 ^d
33	65.2	3.0	6.0	13.1	8.1	1.5	3.1 ^b
34	65.4	3.0	9.0	18.0		1.6	3.0 ^b
35	64.0	3.0	10.0	20.0		1.6	1.5 ^b
36	63.9	3.0	30.0			1.5	1.6 ^b
37	63.8	3.0			30.1	1.5	1.5 ^b
							80.6 ± 5.41

EXAMPLE	ADHESIVE	AMINE	ISO	OLEIC	EO	GMO	OTHER	HMS
38	60.1	3.1	10.0	19.8	5.5	1.5		89.3 ± 4.97
39	58.7	3.0	10.1	19.8	5.8	1.6	1.0 ^b	88.0 ± 0.29
40	61.9	3.0	10.0	20.0	5.0			69.0 ± 3.00
41	60.2	3.0	10.3	20.0	5.0		1.5 ^b	80.0 ± 1.24
42	58.8	3.5	10.1	20.0	5.1	1.5	1.0 ^b	86.0 ± 0.78
43	58.3	4.0	10.2	20.2	5.0	1.5	1.0 ^b	84.0 ± 2.01
44	57.5	4.5	9.9	20.0	5.4	1.5	1.1 ^b	84.0 ± 3.61
45	57.3	5.1	10.1	20.0	5.0	1.5	1.0 ^b	87.0 ± 7.23

AMINE = 1-Isobutyl-1H-imidazo[4,5-c]quinolin-4-amine

ISO = Isostearic acid

OLEIC = Oleic acid

EO = Ethyl oleate

GML = Glyceryl monolaurate (available from Lauricidin, Inc.,
Monroe, Michigan, under the trade designation Lauricidin.

HMS = % Penetration in 24 hours in hairless mouse skin model

* Horizontal shaker placed in 40°C constant temperature room

^b N,N-Dimethyldodecylamine-N-oxide

^c Isopropyl myristate

^d Diisopropyl adipate

- Used 3 independent determinations

EXAMPLES 46-48

Pressure-Sensitive Adhesive Coated Sheet Materials Prepared Using Unmicronized 1-Isobutyl-1H-imidazo[4,5-c]-
55 quinolin-4-amine

Using the general method of Example 18 the formulations shown below were prepared. 1-Isobutyl-1H-imidazo[4,5-c]quinolin-4-amine that had been ground with a mortar and pestle was used. The adhesive was the 93:7 isoctyl acrylate:acrylamide copolymer prepared in PREPARATIVE METHOD 1 above. The solvent was 90:10 ethyl acetate:methanol. All formulations were mixed at room temperature.

5

10

15

		Example		
		46	47	48
	1-Isobutyl-1H-imidazo[4,5-c]quinolin-4-amine	5.0	3.0	3.0
	Ethyl oleate	5.1	5.0	8.0
	Iso stearic acid	10.0	10.0	6.0
	Oleic acid	20.0	20.0	13.0
	Glyceryl monolaurate	1.5	1.5	1.5
	N,N-dimethyldodecylamine-N-oxide	1.0	1.1	3.0
	Adhesive	57.4	59.3	65.4

The formulations of Examples 46, 47 and 48 were tested in the hairless mouse skin model (4 independent determinations per formulation) and the guinea pig model. Unless otherwise stated, patches that measured 2.056 cm² were employed. The cream of Example 1 was run side-by-side with the patches in the guinea pig model. The results are summarized in Table 8.

25

30

35

Formulation	% Penetration in 24 hrs	% Lesion Inhibition	Interferon Level (activity/ml)
Example 46	36.6 ± 0.88	14	700
		86 ^a	4533 ^a
Example 47	39.8 ± 1.44	79	2266
Example 48	30.8 ± 0.88	93 ^a	> 6400 ^a
Example 1		93	> 6400

^a Patches measuring 3.88 cm² were employed.

40

EXAMPLES 49-51

Examples Showing the Effect of Particle Size

45

Using the general method of Example 18 the formulations shown below, containing 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine of different particle size, were prepared and their penetration through hairless mouse skin was measured. The adhesive used was 93:7 isoctyl acrylate:acrylamide copolymer, prepared in PREPARATIVE METHOD 1 above, the solvent used was 90:10 ethyl acetate:methanol, and the formulations were shaken at 40 °C for 72 hours in their preparation. Patches measuring 2.056 cm² were employed and 4 independent determinations were carried out for each formulation.

55

	Example			
	49 ^a	50 ^b	51 ^c	
5	1-Isobutyl-1H-imidazo-[4,5-c]quinolin-4-amine	5.0	5.0	5.0
	Ethyl oleate	5.0	5.2	5.1
	Isostearic acid	10.1	9.9	10.1
	Oleic acid	20.0	20.0	20.0
10	Glyceryl monolaurate	1.5	1.5	1.5
	N,N-Dimethyldodecyl amine-N-oxide	1.0	1.0	1.0
	Adhesive	57.4	57.3	57.4
15	% Penetration in 24 hrs	40.5±1.99	20.1±0.79	67.0±1.33

^a Average particle size of 26.8 microns^b Average particle size of 32.9 microns^c Average particle size of 1.7 microns

20

EXAMPLE 52

A formulation with the same components in the same proportions as Example 49 was prepared using a different method. The 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine was combined with the oleic and isostearic acids and shaken at 40 °C until there was complete dissolution of the 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine. The remaining ingredients were added and shaken a 40 °C for 72 hours. Patches measuring 2.056 cm² were prepared by the general method of Example 18. Three independent determinations were carried out, and the average penetration in 24 hours was found to be 69.7 ± 1.24 percent of the applied dose.

30

EXAMPLE 53

35

A mixture of 2.4734 g 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine 3.3315 g isostearic acid and 6.6763 g oleic acid was prepared. To 1.8738 g of the above mixture was added 2.8750 g of the 93:7 isoctyl acrylate:acryamide adhesive copolymer prepared in PREPARATIVE METHOD 2 above, 0.2548 g of ethyl oleate, 0.0510 g N,N-dimethyl-dodecylamine-N-oxide, 0.0820 g glyceryl monolaurate (from Lauricidin, Inc.) and 14.0457 g of 90:10 ethyl acetate/methanol. The above was shaken for 30 hours at room temperature on a horizontal shaker. Transdermal patches were then prepared generally according to the procedures of Example 18.

45

Claims

46

1. A substantially non-irritating pharmaceutical formulation for topical and/or transdermal administration of the agent 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, which formulation comprises:

(a) 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine in an amount of about 0.5 percent to about 9 percent by weight based on the total weight of said formulation; and

(b) a pharmaceutically acceptable vehicle for said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, which vehicle comprises a fatty acid selected from the group consisting of isostearic acid, oleic acid and a mixture thereof in a total amount of about 3 percent to about 45 percent by weight based on the total weight of said formulation, said formulation being further characterized in that, when tested according to the hairless mouse skin model the formulation provides a penetration of the agent of at least about 10 percent of the total amount of the agent contained in the formulation in 24 hours.

2. A formulation according to Claim 1 wherein said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine is present in an amount of about 1 percent to about 7 percent by weight based on the total weight of said formulation.

3. A formulation according to Claim 1 in the form of a cream, comprising an oil phase and a water phase in admixture, said oil phase comprising:

- (a) 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine;
- (b) said fatty acid or mixture of said fatty acids;
- 5 (c) one or more emollients present in a total amount of about 5 percent to about 30 percent by weight based on the total weight of said formulation;
- (d) one or more emulsifiers selected from the group consisting of a nonionic surface active agent and a trivalent cationic emulsifier and present in a total amount of about 2 percent to about 14 percent by weight based on the total weight of said formulation; and
- 10 (e) one or more thickeners present in a total amount of about 3 percent to about 12 percent by weight based on the total weight of said formulation; and
- said water phase comprising water in an amount of about 45 percent to about 85 percent by weight based on the total weight of said formulation.

4. A formulation according to Claim 1 in the form of an ointment comprising:

- 15 (a) 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine in an amount of about 0.5 percent to about 5 percent by weight based on the total weight of said formulation;

(b) a fatty acid selected from the group consisting of isostearic acid, oleic acid and a mixture thereof in a total amount of about 3 percent to about 25 percent by weight based on the total weight of said formulation; and

- 20 (c) a pharmaceutically acceptable ointment base in an amount of about 60 percent to about 95 percent by weight based on the total weight of said formulation.

5. A formulation according to Claim 1, wherein said pharmaceutically acceptable vehicle further comprises a pressure-sensitive acrylic adhesive copolymer comprising, as a major constituent, a hydrophobic monomeric acrylic or methacrylic acid ester of an alkyl alcohol, the alkyl alcohol containing 4 to 10 carbon atoms, said copolymer being present in an amount of about 55 percent to about 85 percent by weight based on the total weight of said formulation.

6. A formulation according to Claim 5 in the form of a pressure-sensitive adhesive-coated sheet material comprising:

- (a) a flexible backing; and

- 30 (b) a pressure-sensitive adhesive coating adhered to one surface of said backing and comprising a mixture of:

i) an acrylic copolymer comprising, as a major constituent, a hydrophobic monomeric acrylic or methacrylic acid ester of an alkyl alcohol, the alkyl alcohol containing 4 to 10 carbon atoms;

ii) 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine in an amount of about 0.5 percent to about 9 percent by weight based on the total weight of said adhesive coating; and

iii) a fatty acid selected from the group consisting of isostearic acid, oleic acid or a mixture thereof, said fatty acid being present in a total amount of about 10 percent to about 40 percent by weight based on the total weight of said adhesive coating.

7. A formulation according to Claim 6, wherein said acrylic copolymer comprises A and B Monomers as follows:

A is a hydrophobic monomeric acrylic or methacrylic acid ester of an alkyl alcohol, the alkyl alcohol containing 4 to 10 carbon atoms, said A monomer being present in an amount by weight of about 80 percent to about 98 percent based on the total weight of all monomers in said copolymer; and

B is a reinforcing monomer selected from the group consisting of acrylic acid, methacrylic acid, an alkyl acrylate or methacrylate containing 1 to 3 carbon atoms in the alkyl group, acrylamide, methacrylamide, a lower alkyl-substituted acrylamide, diacetone acrylamide, N-vinyl-2-pyrrolidone, a vinyl ether, a substituted ethylene and a vinyl ester, said B monomer being present in an amount of about 2 percent to about 20 percent based on the total weight of all monomers in said copolymer.

8. A formulation according to Claim 1, wherein said pharmaceutically acceptable vehicle further comprises a pressure-sensitive acrylic adhesive copolymer comprising:

about 60 to about 80 percent by weight of hydrophobic monomeric acrylic or methacrylic acid ester of an alkyl alcohol, the alkyl alcohol containing 4 to about 10 carbon atoms, based on the total weight of all monomers in the copolymer;

about 4 to about 9 percent by weight based on the total weight of all monomers in the copolymer of a

55 reinforcing monomer selected from the group consisting of acrylic acid, methacrylic acid, an alkyl acrylate or methacrylate containing 1 to 3 carbon atoms in the alkyl group, acrylamide, methacrylamide, a lower alkyl-substituted acrylamide, diacetone acrylamide and N-vinyl-2-pyrrolidone; and

about 15 to about 35 percent by weight of vinyl acetate based on the total weight of all monomers in the

copolymer,

said copolymer being present in an amount of about 55 percent to about 85 percent by weight based on the total weight of said formulation.

9. A formulation according to Claim 6, wherein said adhesive coating further comprises a skin penetration enhancer selected from the group consisting of isopropyl myristate, diisopropyl adipate, ethyl oleate, glyceryl monolaurate, ethyl oleate in combination with glyceryl monolaurate, ethyl oleate in combination with N,N-dimethyldodecylamine-N-oxide, glyceryl monolaurate in combination with N,N-dimethyldodecylamine-N-oxide, and ethyl oleate in combination with both glyceryl monolaurate and N,N-dimethyldodecylamine-N-oxide, said skin penetration enhancer being present in an amount of about 3 percent to about 25 percent by weight based on the total weight of said adhesive coating.

10. Use of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine for the preparation of a medicament for topical and/or transdermal administration to treat a viral disease in a mammal characterised in that the preparation comprises making a formulation according to claim 1.

11. A method of preparing a substantially non-irritating pharmaceutical formulation for topical and/or transdermal administration of the agent 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, which method comprises combining :

(a) 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine in an amount of about 0.5 percent to about 9 percent by weight based on the total weight of said formulation; with

(b) a pharmaceutically acceptable vehicle for said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, which vehicle comprises a fatty acid selected from the group consisting of isostearic acid, oleic acid and a mixture thereof in a total amount of about 3 percent to about 45 percent by weight based on the total weight of said formulation, said method being further characterized in that the components are balanced on combining whereby the formulation, when tested according to the hairless mouse skin model, provides a penetration of the agent of at least about 10 percent of the total amount of the agent contained in the formulation in 24 hours.

30

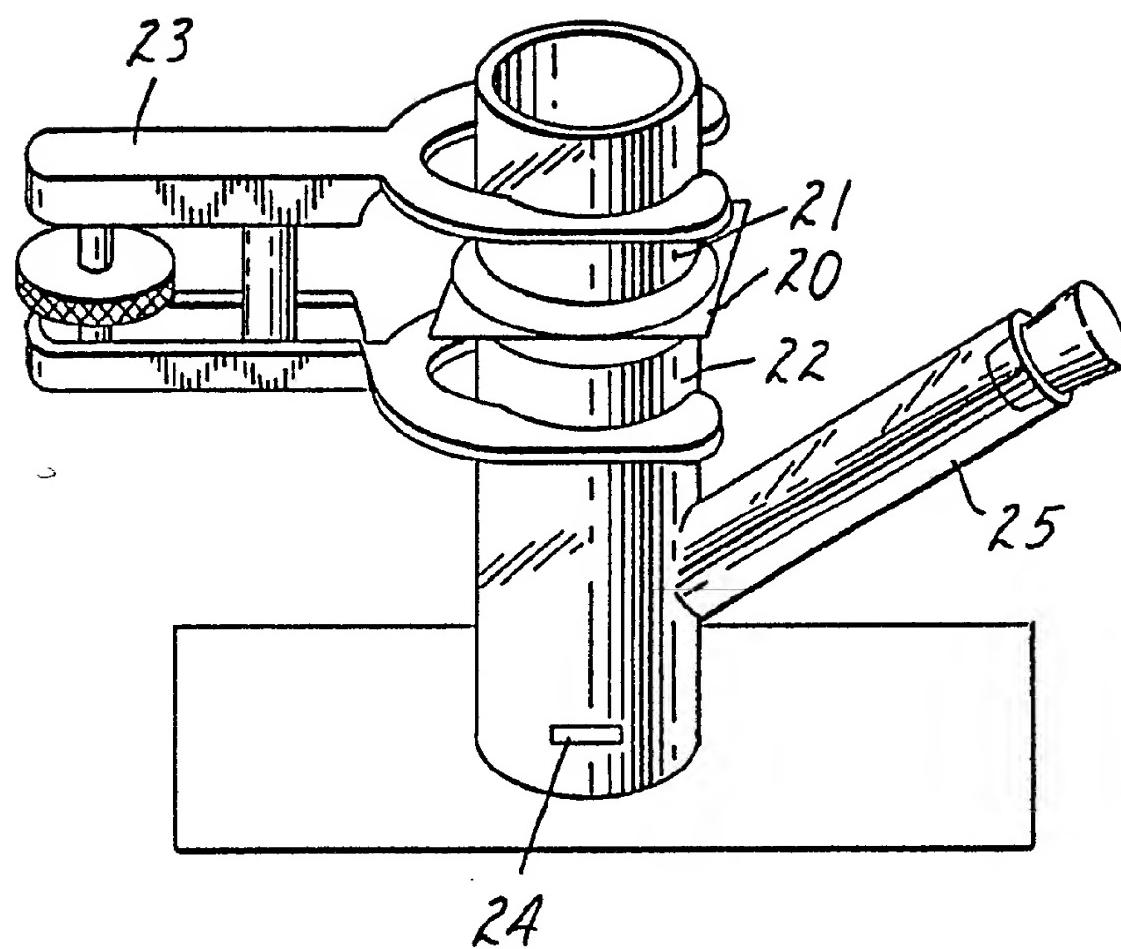
35

40

45

50

55





DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 5)
D,A	US-A-4 689 338 (RIKER) * Claims 1,12,19,22; column 7, lines 3-4; column 8, lines 21-24 and 33-37 * ---	1-4,10-11	A 61 K 31/47 A 61 K 47/12 A 61 L 15/16
A	EP-A-0 196 769 (NEW JERSEY S.U.) * Claims 1,6,8; column 8, lines 61-68; column 9, lines 1-3 * -----	1,5-6,9	
The present search report has been drawn up for all claims			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			A 61 K
Place of search Date of completion of the search Examiner			
THE HAGUE	12-03-1990	SCARPONI U.	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			